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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/942,940	08/31/2001	Han-Mo Koo	38345-174995	8963

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EXAMINER	
DAVIS, MINH TAM B	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 01/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/942,940	KOO ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *2,3,8,11,12,17 and 18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-7,9,10,13-16 and 19-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

It is noted that after review and reconsideration, claims 6, 15 and 21, which have been properly amended to delete the multiple dependency, are rejoined with claims 1, 4-5, 7, 9-10, 13-14, 16, 19-20.

It is further noted that the embodiment of claim 16, drawn to a method for inhibiting growth or recurrent growth of melanoma tumor in a mammal "at risk for melanoma growth or recurrence" is not examined in the instant application.

Since applicant has elected Group I, a method for killing melanoma cells or inducing an antitumor response in a mammal having melanoma, for action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, the embodiments of claim 16, directed to a method for inhibiting growth or recurrent growth of melanoma tumor in a mammal "at risk for melanoma growth or recurrence" have been withdrawn from consideration as being directed to a non-elected invention. See 37 C.F.R. 1.142(b) and M.P.E.P. 821.03. Claim 16 is directed to an invention that is independent or distinct from the invention originally claimed for the following reasons:

A method for inhibiting growth or recurrent growth of melanoma tumor in a mammal "at risk for melanoma growth or recurrence" encompasses a method for preventing melanoma.

The originally elected invention and the above cited embodiment of claim 16 are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). The instant specification does not disclose that these methods would be used together. Further the two methods are distinct, because they have different method objectives, and utilize different products, i.e melanoma patients versus individuals at risk of melanoma, which demonstrates that each method has a different mode of operation.

Furthermore, the distinct products require separate and distinct searches. As such, it would be burdensome to search the two methods together.

Accordingly, claims 1, 4-7, 9-10, 13-16, 19-21 are examined in the instant application.

The following are the remaining rejections.

PRIORITY DATE

The priority date of claims drawn to a method of killing melanoma, using PD184352, such as claims 4, 5, 13, 14, 19, 20, is determined to be 08/31/2001, since the prior application 60/229,290 filed on 09/01/2000 does not recite PD184352, and the data provided by applicant concerning claiming benefit of 60/285690, filed on 04/24/2001 are not consistent with PTO records. Applicant is invited to submit evidence pointing to the serial number, page and line where support can be found establishing an earlier priority date.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

Claims 1, 7, 9-10, 16 remain rejected under 112, first paragraph for lack of a clear written description of an organic small molecule inhibitor of MAPK/ERK kinase for reasons already of record in paper of 04/05/04.

It is clear that since claims 6, 15, 21 depend on claims 1, 9, and 16, respectively, claims 6, 15, 21 would be rejected together with the claims 1, 9 and 16.

Applicant argues that the claims inhibitors are all noncompetitive inhibitors of MEK, as recited in the amended claims, and that as an additional limitation, although not recited in the claims, these inhibitors share a common/overlapping binding site in MEK.

Applicant's arguments in paper of 11/08/04 have been considered but are found not to be persuasive for the following reasons:

There is no common structure among the claimed inhibitors, which could be peptide or non-peptide non-competitive inhibitors of MEK, that bind to any site on MEK, because the claims are not limited to non-competitive inhibitors of MEK that bind to a specific site on MEK. In addition, even if the claims are limited to non-competitive inhibitors of MEK that bind to a specific site on MEK, the structure of the claimed numerous small molecule noncompetitive inhibitors which bind to said site still could not be predicted, based on the structure of the binding site, especially there is no disclosure on the three dimensional structure of the site.

It is noted that in a recent 2004 court case (*Rochester v. Searle*, 358 F.3d 916, Fed Cir., 2004) recited by Appellant, the court states that "even with the three

dimensional of enzymes such as COX-1 and COX-2 in hand, it may even now not be within the ordinary skill in the art to predict what compounds might bind to and inhibit them".

The present application is similar to that in Rochester case, in that even the structure of the binding site on MEK is known in the art, and except for PD98059, U0126 or PD184352, one cannot predict what the structure of non-competitive inhibitors of MEK in vivo is, especially in view that three dimensional structure of the binding site is not even disclosed in the specification or known in the art

Thus in view that the recited three small inhibitors, PD98059, U0126 or PD184352, although sharing a common/overlapping binding site in MEK, are not representative species of the claimed genus and that the specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus" the claimed invention does not meet the requirement of *Lilly*.

Further, the specification does not disclose "relevant identifying characteristics, functional characteristics which are coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." Thus the claimed invention does not meet the requirement of *Enzo*.

Since the specification fails to adequately describe the product for use in the claimed method , it also fails to adequately describe the claimed method.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

1. Claims 1, 6-7, 9-10, 15-16, 21 are rejected under 112, first paragraph because while being enabling for a method for treating melanoma, using PD98059, U0126 or PD184352, the specification lacks enablement for a method of treating melanoma using "an organic small molecule inhibitor of MAPK/ERK kinase".

It is noted that there is no common structure among the claimed inhibitors, which could be peptide or non-peptide non-competitive inhibitors of MEK. Although the three cited inhibitors share a common/overlapping binding site in MEK, the structure of the claimed small molecule noncompetitive inhibitors which bind to said site could not be predicted.

It is further noted that in a recent 2004 court case (*Rochester v. Searle*, 358 F.3d 916, Fed Cir., 2004) recited by Appellant, the court states that "even with the three dimensional of enzymes such as COX-1 and COX-2 in hand, it may even now not be within the ordinary skill in the art to predict what compounds might bind to and inhibit them".

The present application is similar to that in Rochester case, in that even the structure of the binding site on MEK is known in the art, and except for PD98059, U0126 or PD184352, one cannot predict what the structure of non-competitive inhibitors of MEK in vivo is, especially in view that three dimensional structure of the binding site is not even disclosed in the specification or known in the art.

Because one would not know how to make the claimed numerous small molecule inhibitors for use in the claimed method, one would not know how to make and use the claimed method.

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

2. If Applicant could overcome the above 112, first paragraph, claim 16 is still rejected under 112, first paragraph.

Claim 16 is drawn to a method for inhibiting growth or recurrent growth of melanoma "tumor".

It is noted that tumor encompasses growth that is not necessarily malignant, such as any swelling related to melanoma, or benign melanoma (Stedman's Medical dictionary, p.1652-1653).

Applicant has not taught how to inhibit growth of such claimed melanoma tumors.

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

REJECTION UNDER 35 USC 102(a), NEW REJECTION

Claims 1, 4 are rejected under 35 USC 102(a) as being anticipated by Shellman Y et al, April 2000, J Investigative Dermatology, 114(4): 789.

Claims 1, 4 are drawn to a method of killing melanoma cells, comprising contacting said cells for an effective time with an effective amount of an organic small molecule inhibitor of MAPK/ERK kinase (MEK) enzymes, which inhibitor is a direct, noncompetitive inhibitor of MEK which does not inhibit the binding of the enzymes to one of its substrate, ATP, and induces apoptosis in said cells. Said inhibitor is U0126.

Shellman et al teach that anti-apoptotic defense of melanoma are regulated through multiple signaling pathways, including Ras, P13K, MEK and NF-kB. Shellman et al further teach that multiple inhibitors (ras inhibitor, P13K inhibitor, MEK inhibitor U0126, and NF-kB inhibitor), using alone either directly induced cell death, or potentiated cisplatin-induced apoptosis to different degrees of cultured melanoma cells.

REJECTION UNDER 35 USC 103, NEW REJECTION

Claims 1, 4-7, 9-10, 13-16, 19-21 are rejected under 35 USC 103 as being obvious over Shellman Y et al, supra, in view of US 6,147,107, Sebolt-Leopold JS et al, 1999, Nature Medicine, 5(7): 810-816, and Hoshino, R, et al, 1999, Oncogene, 18: 813-822.

Claims 1, 4-5, 7, 9-10, 13-14, 16, 19-20 are drawn to a method of killing melanoma cells, or melanoma tumor in a mammal, or a human, comprising contacting said cells for an effective time with an effective amount of an organic small molecule inhibitor of MAPK/ERK kinase (MEK) enzymes, which inhibitor is a direct, noncompetitive inhibitor of MEK which does not inhibit the binding of the enzymes to one of its substrate, ATP, and induces apoptosis in said cells. Said inhibitor induces apoptosis in said cells, thereby inducing an antitumor response that comprises (i) at least 50% decrease in tumor size measured as the sum of the products of maximal perpendicular diameters of all measurable lesions,(ii) absence of new lesions, and (iii) lack of progression of any preexisting lesions. Said inhibitor is PD98059, U0126 or PD184352.

Shellman et al teach that anti-apoptotic defense of melanoma are regulated through multiple signaling pathways, including Ras, P13K, MEK and NF-kB. Shellman et al further teach that multiple inhibitors (ras inhibitor, P13K inhibitor, MEK inhibitor U0126, and NF-kB inhibitor), using alone either directly induced cell death, or potentiated cisplatin-induced apoptosis to different degrees of cultured melanoma cells.

Shellman Y et al do not teach the MEK inhibitor PD98059, or PD184352. Shellman Y et al do not teach treating melanoma *in vivo* in a mammal or in human, using PD98059, U0126 or PD184352. Shellman et al do not teach that the MEK inhibitor induces an antitumor response that comprises (i) at least 50% decrease in tumor size measured as the sum of the products of maximal perpendicular diameters of all measurable lesions,(ii) absence of new lesions, and (iii) lack of progression of any preexisting lesions.

Hoshino R et al teach that the MAP kinase is constitutively activated in several human tumors, both in vitro and in vivo, including skin cancer cell line which is strongly activated (type III) (table 1, type II and III on page 817). Hoshino R et al teach that the degree of activation in type III is strong, exceeding 50% of the level of that under growth-stimulation conditions (p.815, first column, last 8 lines of the first paragraph).

US 6,147,107 teaches that PD98059, U0126 and PD184352 are inhibitors specific for MAP kinase (column 8, lines 21-41). US 6,147,107 teaches that treating carcinoma cancer cell line A431 with PD98059 alone results in an overall decrease in proliferative activity, demonstrating that an independent method that blocks MAP kinase function by PD98059 decreases proliferation, and also potentiates the ability of radiation

to kill the cancer cells (column 12, lines 53-64). US 6,147,107 teaches a method for treating cancer in a mammal using any of the three inhibitors PD98059, U0126 and PD184352 in combination with radiation therapy (claim 10).

Sebolt-Leopold JS et al teach that blockade of the MAP kinase pathway suppresses growth of colon cancer in vivo, using an inhibitor of MEK, PD184352. Sebolt-Leopold JS et al teach that the tumor growth is inhibited 53-79% (p.813, first column, second paragraph), and that consistent with cell culture results, the in vivo response to PD 184352 seems to correlate with expression level of the target MAP kinase (p.813, second column, first paragraph).

It is noted that although the art does not teach that the MEK inhibitor PD98059, U0126 or PD184352 induces an antitumor response in melanoma cells, that comprises (i) at least 50% decrease in tumor size measured as the sum of the products of maximal perpendicular diameters of all measurable lesions,(ii) absence of new lesions, and (iii) lack of progression of any preexisting lesions, however, since the art MEK inhibitor is the same as the inhibitor used in the claimed method, one would have expected that they would have the same characteristics and properties.

Although the reference does not specifically teach that the inhibitor induces an antitumor response in melanoma cells, that comprises (i) at least 50% decrease in tumor size measured as the sum of the products of maximal perpendicular diameters of all measurable lesions,(ii) absence of new lesions, and (iii) lack of progression of any preexisting lesions, however, the claimed therapeutic agents appears to be the same as the prior art inhibitor, absent a showing of unobvious differences. The office does not

have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable diffrences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

It would have been prima facia obvious for one of ordinary skill in the art at the time the invention was made to treat melanoma, using an inhibitor of MAP kinase, such as U0126, as taught by Shellman Y et al, because anti-apoptotic defense of melanoma are regulated through multiple signaling pathways, including Ras, P13K, MEK and NF-kB and because multiple inhibitors (ras inhibitor, P13K inhibitor, MEK inhibitor U0126, and NF-kB inhibitor), using alone either directly induced cell death, or potentiated cisplatin-induced apoptosis to different degrees of cultured melanoma cells.

It would have been obvious to use any of the MAP kinase inhibitors such as PD98059, U0126 or PD184352 taught by US 6,147,107, because they all are specific for MAP kinase, as taught by US 6,147,107, and because besides U0126 which kills melanoma cells, PD98059 decreases proliferation, via inhibition of MAP kianse, and also potentiates the ability of radiation to kill cancer cells such as carcinoma cells as taught by US 6,147,107, and PD184352 suppresses growth of colon cancer in vivo, by blocking the MAP kinase pathway, wherein the in vivo response to PD 184352 seems to

correlate with expression level of the target MAP kinase, as taught by Sebolt-Leopold JS et al.

One would have been motivated to treat melanoma in a mammal, or in human with a reasonable expectation of success, because of the following reasons:

1) The MAP kinase inhibitor, such as PD184352, has been used successfully in suppressing growth of colon cancer in vivo, by blocking the MAP kinase pathway, wherein such in vivo suppression of colon cancer cells correlates with in vitro data, as taught by Sebolt-Leopold JS et al,

2) The MAP kinase inhibitors, such as PD98059, U0126 or PD184352 have been used for treating cancer in a mammal in combination with radiation, as taught by US 6,147,107,

3) Anti-apoptotic defense of melanoma are regulated through multiple signaling pathways, including Ras, P13K, MEK and NF-kB, as taught by Shellman Y et al, wherein such mechanistic properties are expected to be the same in vivo and in vitro.

4) The MAP kinase is constitutively and strongly activated in melanoma cell lines, as taught by Hoshino R et al. Since response to the MAP kinase inhibitor PD 184352 seems to correlate with expression level of the target MAP kinase in colon cancer, as taught by Sebolt-Leopold JS et al, one would have expected that response in melanoma cells would be the same as that of colon cancer cells.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JEFFREY SIEW can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MINH TAM DAVIS

January 24, 2005

Susan Ungar Patent Examiner
Primary
SUSAN UNGAR